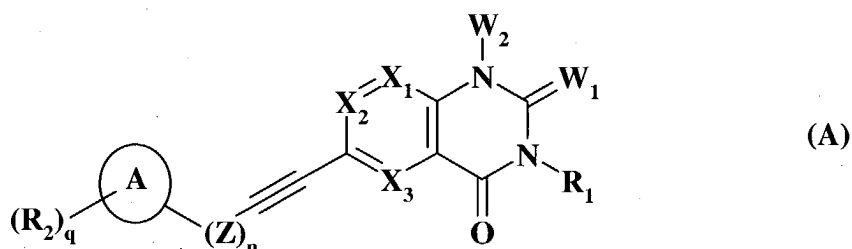


CLAIMS

What is claimed is:

1. A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13 of Formula (A)



or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,
wherein:

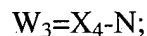
- 10 W_1 is O, S, or NR_3 , wherein R_3 is hydrogen, (C_1-C_6) alkyl, hydroxyl or cyano;
 W_2 is selected from :
- hydrogen;
 - trifluoromethyl;
 - NH_2 ;
 - 15 (C_1-C_{10}) alkylN(H);
 - $[(C_1-C_{10})$ alkyl] $_2N$, wherein each (C_1-C_{10}) alkyl moiety is the same or different;
 - (C_1-C_6) alkyl;
 - (C_3-C_6) alkenyl;
 - 20 (C_3-C_6) alkynyl;
 - phenyl;
 - naphthyl;
 - phenyl- (C_1-C_{10}) alkyl;
 - naphthyl- (C_1-C_{10}) alkyl;
 - 25 (C_3-C_{10}) cycloalkyl- (C_1-C_{10}) alkyl;
 - an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N- (C_1-C_{10}) alkyl;

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

5 wherein in W₂ each (C₁-C₁₀)alkyl, (C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)alkynyl, phenyl, naphthyl, phenyl-(C₁-C₁₀)alkyl, naphthyl-(C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl-(C₁-C₁₀)alkyl, aromatic heterocycle, and nonaromatic heterocycle group is independently unsubstituted or substituted by from 1 to 3 groups, which may be identical or different, selected from halo, NH₂, (C₁-C₁₀)alkylN(H), [(C₁-C₁₀)alkyl]₂N, wherein each (C₁-C₁₀)alkyl moiety is the
10 same or different, cyano, trihalo(C₁-C₆)alkyl, (C₁-C₆)acyl, C(=O)OR₄, -OR₄, and SR₄;

R₄ is hydrogen or (C₁-C₆)alkyl; or

W₂ and W₁ may be taken together to form a diradical group W₂-W₁ of formula



15 W₃ is N or CR₅ wherein R₅ is selected from:

hydrogen;

OR₆;

SR₆;

(C₁-C₆)alkyl;

20 (C₃-C₈)cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

phenyl;

25 naphthyl;

(C₅-C₁₀)heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

phenyl-(C₁-C₁₀)alkyl; and

naphthyl-(C₁-C₁₀)alkyl;

30 R₆ is selected from hydrogen, (C₁-C₆)alkyl, phenyl-(C₁-C₁₀)alkyl, and naphthyl-(C₁-C₁₀)alkyl;

wherein in W_3 each (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10}) heteroaryl, phenyl- (C_1-C_{10}) alkyl, and naphthyl- (C_1-C_{10}) alkyl group is independently unsubstituted or substituted by $(CH_2)_p$ -OH or $(CH_2)_p$ -NH₂;

5 p is an integer of from 0 to 4 inclusive;

X_4 is N or CR₇, wherein R₇ is selected from:

hydrogen;

NR₈R₉;

OR₈;

10 SR₈;

(C_1-C_6) alkyl;

(C_3-C_8) cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N- $(C_1-$

15 $C_{10})$ alkyl;

phenyl;

naphthyl;

(C_5-C_{10}) heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N- (C_1-C_{10}) alkyl;

20 phenyl- (C_1-C_{10}) alkyl; and

naphthyl- (C_1-C_{10}) alkyl;

R₈ and R₉ are the same or different, and are selected from hydrogen;

(C_1-C_6) alkyl; phenyl- (C_1-C_{10}) alkyl; and naphthyl- (C_1-C_{10}) alkyl;

wherein in X_4 each (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, saturated heterocycle,

25 phenyl, naphthyl, (C_5-C_{10}) heteroaryl, phenyl- (C_1-C_{10}) alkyl, and naphthyl- $(C_1-$

$C_{10})$ alkyl group is independently unsubstituted or substituted by $(CH_2)_p$ -OH or $(CH_2)_p$ -NH₂, wherein p is an integer from 0 to 4 inclusive;

X_1 , X_2 and X_3 independently of each other are N or C-R, wherein R is selected from:

30 hydrogen;

(C_1-C_6) alkyl;

hydroxyl;

(C₁-C₆)alkoxy;

halo;

trifluoromethyl;

cyano;

5 nitro;

S(O)_{n₁}R₄, wherein R₄ is as defined above;

NR₁₀R₁₁;

n₁ is an integer of from 0 to 2 inclusive;

R₁₀ and R₁₁ are the same or different, and are independently selected from

10 hydrogen;

(C₁-C₆)alkyl;

phenyl-(C₁-C₁₀)alkyl; and

naphthyl-(C₁-C₁₀)alkyl; or

15 R₁₀ and R₁₁ may be taken together with the nitrogen atom to which they are
bonded to form a 5-membered or 6-membered ring containing carbon atoms,
the nitrogen atom to which R₁₀ and R₁₁ are attached, and optionally a second
heteroatom selected from O, S, N(H), and N(C₁-C₁₀)alkyl,

wherein not more than two of the groups X₁, X₂, and X₃ simultaneously are a
nitrogen atom;

20 n is an integer of from 0 to 8 inclusive;

Z is C(R₁₂)(R₁₃);

Each R₁₂ and R₁₃ independently of each other are selected from:

hydrogen;

(C₁-C₆)alkyl;

25 trihalo(C₁-C₆)alkyl;

halo;

NH₂;

(C₁-C₆)alkylN(H);

30 [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety is the same or
different;

OR₄;

SR₄; and

$C(=O)OR_4$, wherein R_4 is as defined above; or

R_{12} and R_{13} on the same carbon atom may be taken together with the carbon atom to which they are attached to form a carbonyl group; and

Z can contain 1 carbon-carbon double bond when two R_{12} groups are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon double bonds when four R_{12} groups are absent or three R_{12} and one R_{13} groups are absent and n is an integer of from 3 to 8; and

Z can contain 1 carbon-carbon triple bond when two each of R_{12} and R_{13} are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon triple bonds when four each of R_{12} and R_{13} are absent and n is an integer of from 4 to 8; and

One $C(R_{12})(R_{13})$ group in Z can be replaced with O, N(H), N(C_1 - C_6)alkyl, S, S(O), or S(O)₂;

A is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N(C_1 - C_{10})alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N(C_1 - C_{10})alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N(C_1 - C_{10})alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N(C_1 - C_{10})alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0

5 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

Each R₂ may be the same or different, and is independently selected from:

hydrogen;

(C₁-C₆)alkyl;

halo;

10 cyano;

nitro;

trihalo(C₁-C₆)alkyl;

NR₁₀R₁₁;

OR₁₄;

15 SR₁₄;

S(O)R₁₄;

S(O)₂R₁₄;

(C₁-C₆)acyl;

(CH₂)_kNR₁₀R₁₁;

20 X₅(CH₂)_kNR₁₀R₁₁;

(CH₂)_kSO₂NR₁₄R₁₅;

X₅(CH₂)_kC(=O)OR₁₄;

(CH₂)_kC(=O)OR₁₄;

X₅(CH₂)_kC(=O)NR₁₄R₁₅;

25 (CH₂)_kC(=O)NR₁₄R₁₅; and

X₆-R₁₆;

X₅ is O, S, N(H), or N(C₁-C₆)alkyl;

k is an integer of from 0 and 3 inclusive;

R₁₀ and R₁₁ are as defined above;

30 R₁₄ and R₁₅ may be the same or different, and independently are hydrogen or (C₁-C₆)alkyl;

X₆ is a single bond, -CH₂-, O, or S, S(O), or S(O)₂;

R₁₆ is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

cyclopentyl;

cyclohexyl; and

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

wherein in R₁₆ each phenyl, aromatic 5-membered or 6-membered, heterocyclic ring, cyclopentyl, cyclohexyl, and non-aromatic 5-membered or 6-membered heterocyclic ring group independently is unsubstituted or substituted with from 1 to 3 groups independently selected from (C₁-C₆)alkyl, halo, trihalo(C₁-C₆)alkyl, hydroxyl, (C₁-C₆)alkoxy, SH, (C₁-C₆)alkylthio, NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different;

q is an integer of from 0 to 7 inclusive;

R₁ is a group selected from:

hydrogen;

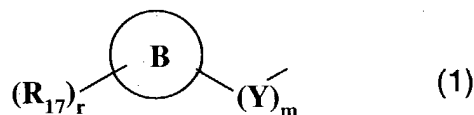
(C₁-C₆)alkyl;

(C₃-C₆)alkenyl; and

(C₃-C₆)alkynyl,

wherein in R₁ each (C₁-C₆)alkyl, (C₃-C₆)alkenyl, and

(C₃-C₆)alkynyl group is independently unsubstituted or substituted with from 1 to 3 groups independently selected from NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different, (C₁-C₆)alkyl, cyano, trihalo(C₁-C₆)alkyl, C(=O)OR₄, OR₄, SR₄, wherein R₄ is as defined above, and a group of formula (1)



m is an integer of from 0 to 8 inclusive,

Y is $\text{CR}_{18}\text{R}_{19}$;

Each R_{18} and R_{19} independently of each other, is selected from:

- hydrogen;
- 5 (C₁-C₆)alkyl;
- phenyl;
- trihalo(C₁-C₆)alkyl;
- halo;
- NH₂;
- 10 (C₁-C₆)alkylN(H);
- [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different;
- OR₄;
- SR₄; and
- 15 C(=O)OR₄;
- R₄ is as defined above;

Y can contain 1 carbon-carbon double bond when two R_{18} groups are absent and m is an integer of from 2 to 8; and

- 20 Y can contain 2 carbon-carbon double bonds when four R_{18} groups are absent or three R_{18} and one R_{19} groups are absent and m is an integer of from 3 to 8; and

Y can contain 1 carbon-carbon triple bond when two each of R_{18} and R_{19} are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon triple bonds when four each of R_{18} and R_{19} are absent and m is an integer of from 4 to 8; and

- 25 One $\text{C}(\text{R}_{18})(\text{R}_{19})$ group in Y can be replaced with O, N(H), $\text{N}(\text{C}_1\text{-C}_6)\text{alkyl}$, S, S(O), or S(O)₂;

B is a group selected from:

- phenyl;
- an aromatic 5-membered or 6-membered monocyclic heterocycle
- 30 comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and $\text{N}(\text{C}_1\text{-C}_{10})\text{alkyl}$;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

naphthyl;

5 an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

10 an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl; and

15 a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

20 r is an integer of from 0 to 7 inclusive,

Each R₁₇ may be the same or different and independently is selected from:

hydrogen;

(C₁-C₆)alkyl;

halo;

25 cyano;

nitro;

trihalo(C₁-C₆)alkyl;

NR₁₀R₁₁;

OR₁₄;

30 SR₁₄;

S(O)R₁₄;

S(O)₂R₁₄;

(C₁-C₆)acyl;

(CH₂)_kNR₁₀R₁₁;

X₅(CH₂)_kNR₁₀R₁₁;

(CH₂)_kSO₂NR₁₄R₁₅;

5 X₅(CH₂)_kC(=O)OR₁₄;

(CH₂)_kC(=O)OR₁₄;

X₅(CH₂)_kC(=O)NR₁₄R₁₅;

(CH₂)_kC(=O)NR₁₄R₁₅; and

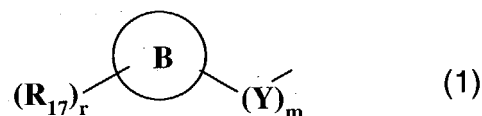
X₆-R₁₆, wherein X₅, k, R₁₀, R₁₁, R₁₄, R₁₅, X₆, and R₁₆ are as defined above.

10 2. The combination of Claim 1, wherein:

W₂ is (C₁-C₆)alkyl;

W₁ is O; and

R₁ is a group of formula (1)



15 wherein Y, B, R₁₇, m, and r are as defined for Formula (A) in Claim 1.

3. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
20 dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-
quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;

25 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-
pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

5 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

10 4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid;

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

4. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

15 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

20 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

25 4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

30 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid.

5. A pharmaceutical composition, comprising a combination of valdecoxib,
5 or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of
MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically
acceptable carrier, diluent, or excipient.
6. A method of treating a disease or disorder selected from cartilage damage,
10 inflammation, arthritis, and pain in a mammal, comprising administering to the
mammal a therapeutically effective amount of a combination of valdecoxib, or a
pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of
MMP-13, or a pharmaceutically acceptable salt thereof.
- 15 7. The method according to Claim 6, wherein the disease or disorder is
rheumatoid arthritis.
8. The method according to Claim 6, wherein the disease or disorder is
osteoarthritis.
- 20 9. The method according to Claim 6, wherein the disease or disorder is joint
inflammation.
10. The method according to Claim 6, wherein the pain is joint pain.